Risk of brain cancer from exposure to radiofrequency fields in childhood and adolescence

Final Report Summary - MOBI-KIDS (Risk of brain cancer from exposure to radiofrequency fields in childhood and adolescence)

Executive Summary:
The overall objective of the current project was to assess the potential carcinogenic effects of childhood and adolescent exposure to radio frequency (RF) and extremely low frequency (ELF) from mobile telephones on tumours of the central nervous system
In order to achieve this, the operational objectives were:
- To conduct a multinational epidemiological case-control study of brain tumours diagnosed in young people in relation to electro-magnetic fields (EMF) exposure from mobile telephones and other sources of RF in eight countries under the current grant, and, subject to funds being secured separately, in a number of non-European countries;
- To develop and validate improved indices of RF and extremely low frequency (ELF) exposure, and assess related uncertainties, for all subjects in the study;
- To analyse the relation between risk of brain tumours and exposure to RF and ELF from mobile phones and other relevant and important sources of exposure in young people's general environment.
The MOBI-KIDS project was conducted in 14 countries (Australia, Austria, Canada, France, Germany, Greece, India, Israel, Italy, Japan, Korea, New Zealand, Spain, The Netherlands) between 2010 and 2015. It used a case-control study design, recruiting 898 eligible cases aged 10 to 24 years old and 1 912 controls matched to the cases on reference date, study region and age.
Each participant completed a face-to-face interview that included information on socio-demographic factors; complete residential history; exposure to farm and domestic animals; mobile phone use; use of other wireless communication devices including cordless phones and Wi-Fi; exposure to other environmental and occupational sources of EMF; occupational history of the subject and his/her parents during the peri-conception, pregnancy and peri-natal periods; occupational exposures to ionising radiation and chemicals; medical radiation exposure; medical history of the subject and mother and water and disinfection by-products exposure (the later only in 6 countries). Interviewers completed a questionnaire regarding responsiveness of the interviewee and quality of recall. Validation studies were conducted, as well as various sub studies, to assess the validity and accuracy of the information collected and identify and characterise possible recall and selection biases which may affect the interpretation of study results. Extensive work went into characterising, modelling and validating ELF and RF exposure from different types of mobile and cordless phones, different communication systems and other environmental sources of EMF. The mobile and cordless phones ELF and RF algorithms, to estimate amount of exposure at the location of the tumour, have been completed and validated. Estimation of occupational and environmental exposures to EMF and other factors is underway.
Most brain tumours were of the neuroepithelial type, mainly gliomas. Mean age of cases and controls at the reference date is 16.53 and 16.67 respectively, with 56% of male participants. There were similar proportions of childhood (10-14), adolescent and young adult cases and controls. Tumour localisation was made by neuro radiologists in each country, using standardised age-specific 3D grids, for over 90% of cases. Validation of tumour localisation and of diagnosis is underway.
Among regular users of mobile phones, the mean time since start of mobile phone use was 6.2 years for controls, with high differences by age group: 3.2 years for the younger age group (10-14) and 9.2 years for the older age group (20-24), respectively; in the latter group, 37% of controls reported using a phone for 10 years or more. Average number of calls per month was 43 for cases and 49 for controls – with 5% of cases and 4% of controls making more than 10 calls per day on average –, and average hours per month talking on the mobile phone were 2.1 and 2.6 respectively – 4% of case and 3% of controls used the phone for calling more than 1 hour per month on average. In both indicators of mobile phone use, we observed an increasing trend in number of calls and average call time with age.
Analyses of the association between mobile phone use and brain tumour risk, as well as between estimated RF and ELF exposure at the location of the tumour and risk of brain tumour have been conducted and a publication is in preparation. Results however cannot be made public until publication in a peer-reviewed scientific journal.
This is by far the largest epidemiological study on the effects of EMF on brain tumour risk in young people.

Project Context and Objectives:
CONTEXT
The very rapid worldwide increase in mobile phone use in the last decade, with more than 6 billion subscriptions to date(ITU - ICT Data and Statistics division, 2015), has generated considerable interest in the possible health effects of exposure to radio frequency (RF) fields. In the last 15 years, numerous epidemiological studies of the possible health effects of these exposures have been conducted and published.
In 2011, the International Agency for Research on Cancer (IARC) Monographs on Carcinogenic Risks to Humans(IARC (International Agency for Research on Cancer), 2013) reviewed the epidemiological and experimental evidence and concluded that RF-EMF was a possible carcinogen (group 2B), based on limited evidence in humans and limited evidence in experimental animals.
The epidemiological evaluation mainly relied on the results of two large scale case-control study – a large study in Sweden led by Hardell and collaborators (Hardell et al, 2013b, 2013a) and INTERPHONE, a multinational collaborative study funded by the EC and coordinated by IARC (Cardis et al, 2007, 2007, 2011a; INTERPHONE Study Group, 2011). The Hardell study showed increased risk of malignant brain tumours in relation to amount and duration of use of both mobile and cordless telephones, with risks highest for those who started use before the age of 20.
INTERPHONE analyses included 2708 glioma and 2409 meningioma and 1105 acoustic neuroma cases and their matched controls from 13 countries. A reduced OR related to ever having been a regular mobile phone user was seen for glioma (OR 0.81 95% CI: 0.70 0.94) meningioma (OR 0.79; 95% CI 0.68 0.91) and acoustic neuroma (OR 0.85 95% CI 0.69-1.04) possibly reflecting participation bias or other methodological limitations. No elevated OR was observed 10 or more years after first phone use. Odds ratios, however, were below 1.0 for all deciles of lifetime number of phone calls and nine deciles of cumulative call time. In the tenth decile of recalled cumulative call time, 1640 hours or longer, the odds ratio was 1.40 (95% CI 1.03 1.89) for glioma, 1.15 (95% CI 0.81 1.62) for meningioma and 1.32 (95% CI 0.88–1.97) for acoustic neuroma. With censoring at 5 years before the reference date, in an attempt to take into account the slow growth and possible long diagnostic delay for this disease, the OR for acoustic neuroma in the highest decile of cumulative call time was 2.79 (1.51–5.16). Interestingly, odds ratios for glioma tended to be greater in the temporal lobe (where most of the energy emitted by mobile phone is absorbed) than in other lobes of the brain, and in subjects who reported usual phone use on the same side of the head as their tumour than on the opposite side. Thus, there were suggestions of an increased risk of glioma and acoustic neuroma at the highest exposure levels, but biases and errors prevent a causal interpretation.

Cardis and colleagues investigated the main parameters thought to influence absorption of RF energy in the brain from mobile phone use(Cardis et al, 2011b). This was based on information from the Interphone questionnaire, network operators, laboratory measurements and from software-modified phones issued to a subset of study participants. An algorithm was developed to evaluate the total cumulative RF energy (in joules per kilogram), or dose, absorbed at a particular location in the brain. The main determinants of absorbed energy were the communication system and frequency band, location in the brain and the amount and duration of mobile phone use. Though there was substantial agreement between categorisation of subjects by cumulative absorbed energy and cumulative call time (the exposure variable used in the main Interphone analyses and in many other epidemiological studies), misclassification appeared non-negligible, particularly at higher frequency bands. The algorithm was applied to Interphone Study subjects in five countries (Australia, Canada, France, Israel and New Zealand)(Cardis et al, 2011a). An increased risk of glioma was seen in individuals at the highest quintile of absorbed dose, though relatively few cases were seen in the four lower quintiles. When risk was examined as a function of absorbed dose received in different time windows before diagnosis, an increasing trend was observed with increasing absorbed dose for exposures 7 years or more in the past. Complementary case-case analyses (in which laterality of phone use was not considered to avoid a possible laterality recall bias), also indicated an increased risk in the most exposed region of the brain, based on small numbers of subjects, compared with other areas among long-term users. Patterns of risk for meningioma in relation to absorbed dose were similar, although increases in risk were much smaller than for glioma, and not statistically significant. These results may suggest an increase in risk of glioma in the most exposed area of the brain among long-term and heavy users of mobile phones. However, the exposure algorithm still relies on questionnaire data, and there are uncertainties associated with tumour centre localisation, estimation of absorbed dose, and sample size. These results require replication in an independent and preferably improved setting before they could be taken to indicate a cause-effect relationship.

Of particular concern in recent years has been the growing use of mobile phones among adolescents and, more recently, children: their developing nervous system may be more sensitive to the effects of RF; they are likely to have greater lifetime cumulative exposures to RF from mobile phones than those who started use later in life; further, the spatial distribution of RF energy absorption in anatomical structures of the brain of children and adolescents differs from that of adults and for the same use, maximum SAR tends to be higher in children than adolescents(Wiart et al, 2008).

Because of these concerns, national and international bodies have recommended studies of exposure to children and adolescents as one of the high priority areas for RF research. These include the International EMF Project (WHO, 2006), the research agenda put forward by the EU-funded EMF-NET coordination action (EMF-Net, 2006) and the EFHRAN consortium (EFHRAN Consortium, 2012) as well as national EMF research agendas in many European countries.

Several epidemiological studies are underway or recently completed to study health effects from RF exposures. They include: CEFALO (An international case-control study on brain tumours in children and adolescents and mobile phone use) (Aydin et al, 2011) and studies of mobile phone use in pregnancy and early childhood within existing birth cohorts (GERoNiMO and REMBRANDT projects). CEFALO is the only study that partly addressed the scope of the current project and its design is similar and complementary to that of MOBI-KIDS. Results have recently been published, based on 352 cases and 646 controls (Aydin et al, 2011). The timing of the study (2004-2008) and the choice of age range (7-19 years) were, however, not optimal to study the health impacts of exposure to radiofrequency fields in childhood and adolescence: mobile phone use is now very frequent in children, but in the period 1997-2001 (i.e. 7-8 years before the diagnoses included in the study, assuming a minimum latency of 7-8 years), very few children below the age of 12 years were heavy mobile phone users. Indeed, in CEFALO, very few subjects were long term or heavy users (median years of use 2.7 – only 52 had had a subscription for 4 years or more; median cumulative hours of use lifetime: 35)

Because of the low prevalence of use of mobile telephones in children 5-10 years ago, the rarity of brain tumours in young people and the fact that the cancer risk, if any, related to EMF exposure from mobile phones is expected to be relatively small, inclusion of a large number of countries is essential in order to achieve sufficient power to detect an association between RF exposure and cancer risk if it exists.

AIM AND OBJECTIVES

The overall objective of the current project was therefore to assess the potential carcinogenic effects of childhood and adolescent exposure to radio frequency (RF) from mobile telephones on the central nervous system (CNS). This was precisely the topic of call ENV.2008.1.2.1.1. "Health impacts of exposure to radiofrequency fields in childhood and adolescence", specifically the risk of potential adverse effects in the CNS (e.g. brain cancer) in childhood and adolescence.
In order to achieve the overall objective of the project, MOBI-KIDS had the following operational objectives:
- To conduct a multinational epidemiological case-control study of brain tumours diagnosed in young people in relation to EMF exposure from mobile telephones and other sources of RF in 14 countries: eight countries under the current grant, and, with funds secured separately, in six non-European countries;
- To develop and validate improved indices of RF and extremely low frequency (ELF) exposure, and assess related uncertainties, for all subjects in the study;
- To analyse the relation between risk of brain tumours and exposure to RF and ELF from mobile phones and other relevant and important sources of exposure in the general environment of young people.

The project built upon the methodological experience (both in terms of exposure assessment and epidemiological design) collected within the INTERPHONE study (Cardis et al, 2007), paying particular attention to the issues of potential selection bias related to the very low response rates of population-based controls – by selecting hospitalized controls with specific diagnoses, representative of the general population and unrelated to mobile phone use –; and potential recall errors – by validating questionnaire responses with the help of network operators and repeat questionnaires. Improved exposure indices for RF were derived taking into account spatial distribution of energy in the brain at different ages; ELF from the phones was also considered, as well as other important sources of EMF in the general environment of young people.

Project Results:
The MOBI-KIDS project included five complementary S&T work packages, as follows:.
- WP1: Scientific coordination and conduct of the epidemiological study.
- WP2: Finalisation of the study instruments.
- WP3: Quality assurance.
- WP4: Exposure assessment.
- WP5: Data analysis and management.

WP1 CONDUCT OF THE EPIDEMIOLOGICAL STUDY

A prospective multinational case-control study of brain tumours was conducted in 14 countries around the world (Australia, Austria, Canada, France, Germany, Greece, India, Israel, Italy, Japan, Korea, New Zealand, Spain, The Netherlands). The target study population consists of all persons (males and females) aged 10-24 years who reside in the study regions. In some countries, the study region encompasses the entire country; while in others it has been restricted to defined areas.

Cases were benign and malignant brain tumours, including only tumours that originate in areas of the brain with high exposure to RF and ELF (i.e. exclude tumours originating in the midline). Control selection was in parallel to case ascertainment. The date of surgery of the controls was within + 3 months from the date of surgery of the case (or date of interview if surgery was not performed). Controls were individually matched to cases on age (+-1y for cases less than 17 years and +-2y for cases 17 years and older; the minimum age for controls will be 10 and the maximum 24y at the case's reference date), sex and residency in the same geographical areas as the case.
In order to minimize non-participation, controls were selected among subjects who were operated due to suspected appendicitis, a disease that is common in all age ranges included in the study and not related to mobile telephone use or SES (socioeconomic status). This ensured that the controls were representative of the general population from which the cases arise. Two hospital controls were selected per case.

Overall, a total of 898 cases and 1922 controls were eligible and participated in the study (ANNEX 1 FIGURES 1 and 2). The distribution by country is shown in ANNEX 1I TABLES 1 and 2 and.

The main characteristics of cases and controls recruited are shown in ANNEX 1 TABLE 3. Mean age of cases and controls at the reference data was 16.53 and 16.67 respectively, with 56% of male participants. There were similar proportions of childhood (10-14), adolescent (15-19) and young adult (20-24) cases and controls. More than 84% of the interviews were responded by the index (55%), either alone or with one or both parents. Subjects were judged to be very or fairly cooperative by the interviewer for more than 84% of the interviews.

WP2 – FINALIZATION OF THE STUDY INSTRUMENTS

This WP included the development, testing, finalisation of the core protocol and the different questionnaires used for data abstraction in all countries, information material for study subjects, the procedures for implementing the study, adapted to take into account the specific logistic and legal constraints in each of the participating countries, while maintaining consistency and uniformity of data collection, information material for subjects, the analysis protocol and the tumour localisation protocol.
The study protocol, questionnaire and procedures were completed in 2010/2011 and updated as needed, during the study period, based on input from fieldwork.
A scientific publication describing the study protocol and procedures and specific challenges of the study was published in the scientific literature (Sadetzki et al, 2014).

WP3 – QUALITY ASSURANCE

This WP included ensuring quality of the procedures in place for the conduct of the study, validation of the questionnaire, quality control of the data collected, quality assessment and validation of the exposure estimates, verification of diagnoses and verification of tumour localisation by neuroradiologists.

* Validation of reported mobile phone use (MPU). Two studies were conducted.
-The first compared reported mobile phone use to records of mobile phone use kept by operators for consenting cases and controls. Data were collected from mobile phone operators in countries where this was possible (i.e. Canada, France, Greece, Israel, Korea, Spain, The Netherlands). Agreement between self-reported and recorded MPU was studied both for the number of calls and the duration of calls in the most recent 3 months, 1 year or 2 years prior to the date of interview (none of the operators could provide information on earlier use). Overall, no clear differences in agreement between reported and operator recorded MPU was seen between cases and controls. Number of calls tended to be underreported, and duration of calls overreported as seen in other recent studies, in particular in INTERPHONE (Vrijheid et al, 2009) and the ratio or reported to recorded seemed to increase with increasing average MPU, for both the number of calls and the duration of calls.
- A complementary validation study, funded outside the current grant, included volunteers selected from the general population, as well as consenting control from 12 countries who were provided an Android Smartphone or, if they had their own Android phone, asked to install on their own an application, XMobiSense. The application recorded number and duration of calls, data use, laterality, hands-free device use, and communication system used for both voice calls and data transfer. Results of the pilot study in France, the Netherlands and Spain have been published (Goedhart et al, 2015). As in INTERPHONE(Vrijheid et al, 2006) and the operator validation studies, results indicated that participants on average underestimated the number of calls they made, while they overestimated total call duration. Participants held the phone for about 90% of total call time near the head, mainly on the side of the head they reported as dominant. Results of the full validation study, conducted in 12 countries, with questionnaires administered 6 months – and in some countries 18 months after the use of the application – are being prepared for publication. They provide important information on the accuracy of recall of side of use of the phone and use of hands-free kits, which have been taken into account in the development of the exposure algorithms in WP4. A similar study, with similar results, was also conducted in Japan using a different type of software modified smartphone(Kiyohara et al, In press).

* Validation of diagnosis of brain tumours. A small international group of pathologists is reviewing the histological slides of a sample of 20% of the cases from all countries to validate diagnosis. Results are expected shortly.

* Validation of localisation of brain tumours. A small international group of neuro-radiologists is reviewing the diagnosing images (MRIs) of a sample of cases from all countries to validate tumour localisation. Results are expected shortly.

* Validation of the questionnaire data has been conducted: this involved development and application of data validation tests and checking of consistency data, codes, completion of answers etc. Inconsistencies were referred to the original countries for resolution.

WP4 - EXPOSURE ASSESSMENT

1. DEVELOPMENT OF AN EXPOSURE GRADIENT FOR RF AND ELF
In the absence of clear and consistent data from laboratory or animal study, there is no definite idea of the most appropriate physical quantity to be related to possible health effects of electromagnetic fields radiated from mobile phones. However, it seems reasonable to quantify the exposure in terms of the total energy delivered to the user's body. This energy, in turn, depends on the time of use of the phone, and on the SAR (specific energy absorption rate; i.e. the energy delivered per second to the unit mass of tissue.
While the duration and frequency of use can be deduced from user's interview or from operators' data, the power actually absorbed in the body depends on several factors: some are technical; others are related to the way the phone is used. The importance of these factors was investigated; they included the effective power radiated (influence of power control, time channel occupancy...) and the position of the sources.

The main goal of the exposure assessment project was to develop and implement one (or more) exposure index(es) for each subject in the case-control study based on these factors.

Support to questionnaire development
In a first stage, this WP assisted WP2 in the development of the questionnaire, gathering exposure-relevant information on EMF sources that produce RF and ELF fields. The main emphasis was on hand-held mobile phones (HHPs) using GSM, DECT, WiFi and UMTS protocols, but other, domestic, environmental and occupational sources of RF and ELF that may give rise to exposure levels inside the head comparable to those from HHPs were also considered.
In a second stage, more detailed measurements and calculations were carried out to more precisely quantify the exposure from particular sources so this information can be used in developing the exposure indices.

Work for the quantification of RF and ELF exposures
One of the main goals of the study was to develop improved indices of RF and ELF exposure, and assess related uncertainties. Thus an exposure gradient tool-kit was developed to allocate an ELF and RF exposure index to each case-control subject, to be used as the basis for the study risk assessment. The tool-kit is based on induced current density and specific energy absorption rate (SAR) modelling for ELF and RF exposure respectively, performed as part of the exposure assessment work package. It also takes into account user patterns (from the main questionnaire information collected from the index interview), validation study results (part of MOBI-KIDS, described below) and evolution of communication systems over the duration of the study (information derived from supplementary questionnaires sent out to mobile phone operators).

In order to estimate exposure at the location of the tumour as a function of age, a program called the Gridmaster, which was developed as part of INTERPHONE (Cardis et al, 2011b), was extended for MOBI-KIDS with the addition of the four heterogeneous heads of various ages (8, 11, 14, and 34 year old produced by IT IS (Christ et al, 2010). A reference brain whose volume encompassed all four voxel heads was also defined to help determine exposure at the tumour location as a function of age. Each voxel in this reference brain has a 1 cm3 volume, and the induced current density and SAR in each voxel is given by the corresponding average (from the 1 mm3 modelling) across brain tissues within that voxel.

The following sections describe the different components that contribute to the RF and ELF exposure algorithm for mobile phones, which are shown schematically in FIGURE 1 of ANNEX 2 for ELF (but are very similar for RF).

* Mobile phone communication systems
Within the period of interest for MOBI-KIDS (2000 and 2014) several communication systems were in operation (TABLE 1 of ANNEX 2). Measurements and numerical modelling were performed for each relevant communication system used for voice calls in the period and countries of interest, as well as for non-network communication systems, namely Digital Enhanced Cordless Telecommunications (DECT) and Voice over Internet Protocol (VoIP). Communication systems used for data and not widely used for voice calls, such as Enhanced data rates for GSM evolution (EDGE) and High Speed Packet Access (HSPA), were not included in either the RF or ELF exposure toolkit.

* Typical output power levels
During voice calls mobile phones are able to vary their transmitted power level to reduce interference and extend battery life, a process known as adaptive power control (APC). Because modelling is performed at a fixed power level and the SAR is dependent on the RF transmission power, the SAR values need to be scaled to typical power levels.

The level of transmitted power will also have some effect on the current being drawn from the battery and thus on the ELF magnetic field, particularly for TDMA systems. Therefore, this scaling also applies to the ELF induced current densities. However, this effect is less pronounced for communication systems which emit constantly (as it affects the DC level rather than the ELF) such as UMTS, CDMAOne and CDMA2000.

* Discontinuous Transmission (DTx)
Discontinuous Transmission (DTx), whereby transmission is paused during silent periods, is used during GSM and PDC voice calls to minimise power consumption and interference. In INTERPHONE and in MOBI-KIDS this leads to a reduction in RF duty factor of 30% (Cardis et al, 2011b). In ELF, however, DTx has no material effect on exposure.

* Prevalence of communication systems
There is an estimated order of magnitude difference (at least) in both ELF and RF exposure between GSM and other communication systems, so it is important to know the proportion of time a given communication system is used during voice calls. The prevalence of communication systems is a function of year, mobile phone operator and country. Questionnaires were sent to operators across the different participating countries in order to define the fraction of time a communication system is used for voice calls at time and for operator. Whether a given phone model has the capability of transmitting over communication system was also considered.

* Gridmaster cartographies for mobile communication systems and sub-classifications
Extensive RF numerical modelling work has been undertaken as part of MOBI-KIDS. Eleven different phone classes have been identified, based on the phone shape (e.g. flip, slide; bar, smart phone) and antenna position (top, middle, bottom, external). For each phone class, Gridmaster cartographies are available at the frequencies relevant to the different communication systems of interest.

For ELF, the classification is only done by communication system, except for GSM and (and UMTS), where there is a sub-classification based on phone shape (bar phones versus flip/slide phones). CDMAOne has practically faded out since 2001 (https://www.cdg.org/) and the lack of phones and equipment meant it could not be assessed. However, due to the similarities in communication system between CDMA2000 and CDMAOne with respect to ELF parameters relevant to ELF, it was decided that CDMA2000 be used as a proxy for CDMAOne.

* Usage information
Information on duration, laterality, use of HFKs, texting and uploading data is available from the subject questionnaire. As part of the MOBI-KIDS study, a validation study called Mobi-Expo was undertaken to characterise and validate mobile phone use habits in young people (Goedhart et al, 2015). This was performed using software-modified smartphones (SMSP) which captured information such as communication system used, laterality, duration of calls and use of hands-free kit. Data from this study was used to assign values to these categorical variables.

ELF exposure from text messaging as well as uploading and downloading data (e.g. email, browsing internet) is considered to be negligible due to the large distance between the phone and the head when performing these tasks. For RF, however, numerical modelling at a distance of 33 cm from the head (reading distance as suggested by ophthalmologist) was performed.

* Construction of the ELF and RF algorithms
Both ELF and RF algorithm are very similar since both are based on the INTERPHONE RF algorithm (Cardis et al, 2011b) and many of the parameters relevant to the ELF exposure are also relevant to the RF exposure.

Based on the source and exposure considerations discussed above, the ELF 'dose' is defined by the time weighted average (TWA) current density per month Jmonth_(l,i)at time t_i and location l in the brain: EQUATIONs 1-3 ANNEX 2.

As in INTERPHONE, the lifetime RF exposure is defined by the Cumulative Specific Energy (CSE), given by EQUATION 4 ANNEX 2.

The algorithm for DECT and VoIP are not discussed here but are simplified versions of the one used for network calls.

* Uncertainties in the ELF and RF algorithms
Uncertainties have been estimated for the different parameters in the algorithms, based on the available information from measurements, modelling, literature, and validation studies. In particular, the RF team has estimated the effect of phone position variability in exposure (Ghanmi et al, 2014).

2. EXPOSURE ASSESSMENT FOR OTHER OCCUPATIONAL OR ENVIRONMENTAL FACTORS
Several environmental and occupational agents have been suggested as being associated with brain tumours among children and adults. Among them parental smoking, home and occupational exposure to pesticides and use of hair dyes and sprays. In addition dietary n-nitroso compounds have been linked to the disease as well. Interestingly, little is known about specific risk factors for brain tumours in adolescence, which fall in between the two age groups that have been studied most extensively. It was therefore of importance to collect detailed information on environmental/occupational exposures over life, starting in utero and into adolescence.

Work under this task included the development of a protocol for estimating exposure to chemical, biological and physical agents (ionizing radiation and EMF) from occupational sources. The protocol describes the exposure sources and the available variables to develop exposure metrics, and the tools available to link these exposures to the study population.

Self-reported occupational, residential and school history of the index together with occupational history from parents (3 months prior to conception to three months after birth of index, longest job and any ionising radiation job) has been collected. This information will be used together with Job Exposure Matrices, spatially-resolved environmental pollution data and data provided by drinking water companies or routine monitoring data (disinfection by products) to assess exposure. This generic approach will be made more specific by combining these linkages results with the answers to specific questions from the index persons and their parents (e.g. questions on sources of occupational EMF exposure).

Main exposures of interest
The following exposures are of main interest for study subjects
Ionizing radiation, such as from medical imaging,
Pesticides from occupational use,
Ambient air pollution,
Heavy metals (e.g. lead), from residential or occupational exposure, and
Disinfection by-products from drinking water.

In ANNEX 2 TABLE 2 the agents considered are cross-tabulated with the type of exposure. In the cells the information sources and available tools are depicted for the exposures that we will be able to address. Parental exposure will focus predominantly on occupational and consumption history and not environmental exposures.

Data collected
Self-reported occupational, residential and school history of the index together with occupational history from parents (3 months prior to conception to three months after birth of index, longest job and any job with ionising radiation) has been collected. Data has been translated in ISGLOBAL and sent to centres for checking.

Coding of historical data

The residential and school history data is being geocoded in each centre and will be linked to geocoded exposure information either centrally at ISGlobal, if local ethics allow this to be sent outside of the country, or locally in the participating countries.

For occupational history data, the coding was performed by two independent centres (MU, UU) using two standard classifications of occupations: ISCO-68 and ISCO-88. (ILO 1968; ILO 1990). After merging the data, incongruent codes were identified and consensus between the coders sought. Centres were contacted if the occupational information of an index or the parents was insufficient to be coded. This is the case of Japan and Korea, where efforts were being made to improve the quality of the translations. Nevertheless, the proportion of jobs that could not be coded was less than 5%.

Linkage to exposures

* Air Pollution
Recently, completely spatial resolved surfaces of air pollution have been developed for the priority pollutants (NO2, and PM10) by land use regression incorporating satellite- and ground-based measurements (Vienneau et al, 2013). These surfaces can be linked to the geocoded locations. This process can be done either by sending the geo-coordinates to IRAS or by linkage of the surfaces to the geocodes within the secured environment of ISGLOBAL. The European model has a resolution of a 100m2.

For selected case-control sets the ESCAPE LUR model for NO2, PM2.5 PM10, PMcourse and PMabsorbance can be applied. This will require the extraction of geographical variables (e.g. traffic density, distance major road, distance ports, population density) that will be fed into the ESCAPE prediction algorithms. As this requires active work of a geo-specialist it may not be feasible in all centres in MOBI-Kids. As such these analyses will be at most a sensitivity analysis to the work earlier as to explore if a more refined exposure assessment would have resulted in different results. Resolution of the LUR ESCAPE model is m2 (accuracy depends on the accuracy of the input data).

The above plan limits the analyses to European case-control sets. It is possible to link all cohorts to the Global LUR model as developed by Brauer and colleagues. This newly developed model is an extension of the work that has been performed for the estimation of the global burden of disease project and includes now on top of satellite imaging ground proved exposure data. These models can predict at a 500 m2 resolution. As we would gain only a marginal number of additional cases by NOT restricting to Europe, it is not clear that the use of the global model will pay-off given the larger uncertainties in these global exposure surfaces.

* Occupational exposure
Linkage to existing Job Exposure Matrices (JEMs) will enable translating the job-histories into occupational exposure to chemical, biological and physical agents. The available JEMs are shown in ANNEX 2 TABLE 3. Self-reported information on sources of exposure in the workplace (e.g sources of ELF-MF or ELF-MF) will be combined with the information generated by linking job histories with job exposure matrices in order to derive at a more specific occupational exposure matrix (e.g. lower false positive assignments of exposure).

* Disinfection by-products in drinking water
This is based on questions on consumption of drinking water, showering and swimming practices from the index and maternal questionnaire. Six countries are involved (Spain, Italy, Greece, Canada, New Zealand and Korea). Each centre has sent a standardized questionnaire to water companies or national/regional water authorities to get water disinfection products monitoring data in those instances where the researchers do not have access to central databases of the water companies. To avoid data protection issues, centres used the geocoded residential information and are assigning DBP values themselves, using the water companies' information, and will consequently send the exposure data to the central database at ISGlobal.

- WP5: DATA ANALYSIS AND MANAGEMENT:

This WP included the setting up and maintenance of databases, programming of validation tools and of exposure indices, the analyses of the validation studies, of the non-response questionnaires as well as the main analyses of the relation between the risk of brain tumours and exposures to RF and ELF from mobile phones and other relevant and important sources of exposure in the general environment of young people.

This WP relied on the results of WP1 (the conduct of the case-control study) and WP4 (the estimation of exposure for each of the subjects in the study).

1. DATABASE MANAGEMENT AND DATA VALIDATION AND CLEANING

Databases were developed for:
- the computer assisted interview questionnaire data,
- the follow-up of potential participants
- non-response questionnaires,
- the clinical questionnaire
- the tumour localisation data
- the mobile phone catalogue
- the data from the validation studies.

All databases were closed in December 2015, despite the fact that some are still recruiting for their own purposes. After merging all the interviews from all countries into a main database, containing all the data collected, we checked the dates and diagnoses received, to confirm the eligibility of all participants recruited according to protocol. We took advantage of this process to complete some of the missing information going back to the source countries, and asking them to collect some of these missing variables.

Once the main database was closed, and the checks were done, we developed a tool to perform more validations of dates reported and other important variables from the questionnaire, to confirm their integrity and veracity, based on other data like date of birth, date of diagnosis and so.
All data collected was reviewed to ensure compliance with the core protocol, including case diagnosis, timing of interview, and age criteria. As a result, the following were deemed "ineligible": 432 cases due to a final diagnosis that is not included in our list of eligible tumours; twenty cases that were interviewed more than one year after their date of diagnosis; seventy-one cases who were younger than 10 years old at their date of diagnosis (as the date was earlier than originally thought); two cases who were interviewed before May 2010 and thus considered pilot interviews; and one case who resides outside the defined study region.

2. ANALYSIS

An analysis protocol was developed in WP2 by the Analysis Task Group. It set forth the analytical strategy for the study including rules for imputing missing data and data reported as ranges.

Based on the Analysis protocol, algorithms were programmed to estimate mobile phone use variables including total duration of mobile phone use, total number of calls, duration of use. All variables were calculated up to 1 year before the reference date – date of diagnosis of the case for both the case and his/her matched control. Call time and number of calls were also calculated in windows of time before the reference date (1-4, 5-9 and 10+ years) taking into account, where appropriate, use of hands-free devices.

The ELF and RF algorithms from WP4 were programmed and validated. Descriptive analyses are included in the WP4 algorithm manuscript under preparation.

The final numbers of interviewed and eligible subjects were 898 cases and 1922 controls were eligible and participated in the study (ANNEX 1 FIGURES 1 and 2). Most brain tumours were of the neuroepithelial type, mainly gliomas (ANNEX 1 TABLE 4). Tumour localisation was made by neuro radiologists in each country, using standardised age-specific 3D grids, for over 90% of cases.

Among regular users of mobile phones, the mean time since start of mobile phone use was 6.2 years for controls, with high differences by age group: 3.2 years for the younger age group (10-14) and 9.2 years for the older age group (20-24), respectively; in the latter group, 37% of controls reported using a phone for 10 years or more. Average number of calls per month was 43 for cases and 49 for controls – with 5% of cases and 4% of controls making more than 10 calls per day on average –, and average hours per month talking on the mobile phone were 2.1 and 2.6 respectively – 4% of case and 3% of controls used the phone for calling more than 1 hour per month on average. In both indicators of mobile phone use, we observed an increasing trend in number of calls and average call time with age.

Analyses of the association between mobile phone use and brain tumour risk, as well as between estimated RF and ELF exposure at the location of the tumour and risk of brain tumour have been conducted and a publication is in preparation. Results however cannot be made public until publication in a peer-reviewed scientific journal.

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Potential Impact:
1. POTENTIAL IMPACT

MOBI-KIDS addressed the topic ENV.2008.1.2.1.1. within the Environment 2008 Work Programme. Indeed, and was designed to evaluate the "Health impacts of exposure to radiofrequency fields in childhood and adolescence."

More specifically, MOBI-KIDS aimed "to investigate whether prolonged exposure to radiofrequency fields (RF, EMF) and pulsed low frequency magnetic fields via mobile phone use in childhood and adolescence increases the risk of potential adverse effects in the central nervous system (e.g. brain cancer)"

MOBI-KIDS approached this issue by conducting a multinational epidemiological case-control study of brain tumours diagnosed in young people in relation to exposure to mobile telephones and other sources of RF in 13 countries, taking into account potential confounders, as described in WP2.

MOBI-KIDS also addressed an important gap, identified by numerous national and international agencies, the need for improved EMF exposure assessment for epidemiological studies. Indeed, as described in WP4, the project developed and validated improved algorithms for estimating RF and ELF exposure from mobile communication devices as well as from other environmental and occupational sources. These algorithms were applied to all of the subjects in the MOBI-Kids study and uncertainties were assessed.

Another important impact of the Project was the strengthening of multi-disciplinary and international collaboration in EMF research. MOBI-KIDS built upon the experience of, and difficulties encountered in, the INTERPHONE study, including not only some of the key international participants in INTERPHONE but also a number of new partners with substantial experience in epidemiology and EMF exposure assessment: in designing this study, major efforts were made to improve on the design of INTERPHONE, including overcoming difficult epidemiological problems related to selection bias and recall errors and improving and optimising the exposure assessment both for RF and ELF. Because brain tumours in children, adolescents and young people are rare, and because the effect of EMF exposures from mobile phones, if any, is expected to be small, studies in single countries will generally lack sufficient statistical power to evaluate the possible relation between these exposures and the risk of brain tumours. Only careful large-scale collaborative studies, with detailed exposure assessment and major efforts to avoid and characterise possible biases will therefore be able to answer the question of this call.

Overall, the project brought together epidemiologists, physicists, engineers, clinicians, statisticians and communication specialists from 13 countries - not only from EU countries, but also one associated country (Israel) and, with their own funding, five non-EU countries (Australia, Canada, Japan, Korea and New Zealand). The epidemiological study was carried out in all countries based on a common core protocol and four of the countries (France, Japan, Korea and the UK) collaborated to improve estimates of ELF and RF exposure, clearly demonstrating the international collaboration dimension of the topic. In total, the study provides a truly international perspective to the results obtained.

The results of the MOBI-KIDS project, expected to be published in 2017, will have important implications to support developing Community public health measures and policies. Proactive communication will be established with authorities and policymakers, so as to ensure that the results will be displayed in a form and time that is useful for them to perform their regulatory endeavours. Results will also be useful to another EC funded project, GERoNiMO, providing a solid basis for the evaluation of the potential health impact of mobile communication devices in Europe and the development of recommendations, if needed, for non-technological means of reducing exposures.

2. MAIN DISSEMINATION ACTIVITIES
Throughout the project and in the next years following its completion the objectives of the project are to:
- Update the scientific community about the rationale, concept and results of the MOBI-Kids study
- Raise public awareness about the current state of science in the discussion on mobile phone exposure and heath especially in children and adolescents.
- Inform the patients about the progress of the study and, when available, on its results
- Inform the stakeholders, decision makers and experts in the public health field about the background, design and the results of the study.

To achieve these aims, apart from scientific publications, a wide range of dissemination tools and activities were used to address the stakeholders outside the scientific community and the general public. They can be classified into the following categories: news (radio, TV, newspapers etc.), scientific conferences and publications, press releases and other (such as workshops or engagement events with school children). All the communication tools developed have been extensively used during the course of the project with a total of 135 activities carried out during the entire period.

They main tool for internal and external communication and dissemination was and remain the project website. It was launched in 2009 and has been updated regularly throughout the project. The website is divided into two levels of information: public and private. The public section provides an introduction about the project including a frequently asked questions (FAQ), acknowledges the European Commission funding, describes the main tasks and objectives of the different work packages and includes news and events related to the project. As a special feature, a section called "feature of the month" was added during the course of the study. This feature presents the different cooperating institutes showing their role in MOBI-Kids, specific research interests and country-specific information. The internal area is mainly used as a repository of relevant internal documents, contact details of all partners, meetings information and dissemination materials. Forums were also enabled to enhance communication amongst partners.

To further raise public awareness about the project, the MOBI-Kids study was presented during scientific conferences, meetings of stakeholders, and in media targeting the general public. In several countries (e.g. Germany, Israel, Spain) an additional version of the study flyer specifically designed for children was created. This flyer aimed to ensure that also the youngest receive appropriate information about the study.

In addition, other stakeholders were continuously kept informed about the study. In different participating countries, the background, aims, and methods of the study were presented at national conferences of neurosurgeons, oncologists, neuro-oncologists, and among stakeholders in the fields of electromagnetic fields and epidemiology/public health. The study was also presented to the scientific community at international level, for example at the ICNIRP (International Commission on Non-Ionizing Radiation Protection) conference on non-ionizing radiation and children's health, at the International Congress on Radiation Research or the ISEE (International Society for Environmental Epidemiology) congress.

Information about the study has been furthermore spread among the general public. In different countries TV or radio programmes informed about the study, e.g. through interviews with researchers of the study. Major newspapers have published articles or interviews with project members. This has been the case especially for France and Spain due to the project coordination being in Spain and having more impact on local press.

The first press release was published and 2009 in all participating countries to inform the public about the start of the study. Also in 2009, a project flyer providing general information about the study was developed within the consortium. It was translated into the main languages of the collaborating centres and widely distributed in the respective countries. A second press release announcing the start of the field phase was published in Germany in January 2011.

Regarding the dissemination and exploitation of the results, since the final analyses are ongoing, the main results of the study are not published yet. Documents to inform the general public about the main results of the study will be prepared as soon as the final results are available. Due to the widespread usage of communication devices such as mobile phones, the results of the study regarding potential detrimental health effects will most likely receive a considerable degree of public attention and can potentially have significant societal implications. So far, the extensive use of very different means of communication has contributed to increase the public understanding regarding electromagnetic fields and their potential impact on health.

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